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OPENING ADDRESS*

Nineteenth Graduate Fortnight

GEORGE BAEHR

President, The New York Academy of Medicine

THE Graduate Fortnights were established by the Academy in 1928 upon the recommendation of its Committee on Medical Education in appreciation of the periodic need by all practicing physicians for an intensive review of recent advances in the major branches of medicine. Each year a new subject is selected for the theme of the Fortnight. The special field is covered completely within that period by a combined program of morning, afternoon and evening exercises consisting of lectures, demonstrations, exhibits, hospital clinics, seminars and round table discussions. The entire medical profession is eligible to participate. As lecturers and discussion leaders, the Academy assembles the most outstanding authorities in the country.

The scientific exhibits of the Fortnight represent the contributions of many medical schools, teaching hospitals and research laboratories. This year an attempt has been made to group the exhibits according to subject matter rather than by participating institutions, so as to take the most complete advantage of their educational values. It would be

* Given October 7, 1946 at the opening of the Fortnight.

helpful to the Committee on Medical Education and to me, if Fellows of the Academy and visiting physicians will comment on the new arrangement and give us the benefit of their suggestions for future improvement.

When this beautiful building was erected in 1926, adequate provision was made for the Academy's great Library and for its lecture halls and conference rooms. However, the need for exhibit space was completely overlooked. As a result, we have been obliged to set up our educational exhibits in space which we require for meetings, conferences and the every day work of the Academy's many study committees. Throughout the Fortnight, even the halls and corridors of the lower floors are obstructed with valuable exhibits for which we can find no other room.

There is great need for independent space for these educational exhibits and for many other scientific exhibits which should be continued throughout the year, such as the valuable exhibit of drugs now housed temporarily on the second floor. There is also a growing need for additional space for other expanding activities of the Academy's Committee on Medical Education so that educational opportunities similar to those of the Fortnight can be offered through the year not only to the medical profession but also, from time to time, to the general public.

For this purpose, the Academy has acquired three small tenement buildings on the south side of 103rd Street, immediately adjacent to this building. The additional ground space, to which 30 feet in the present building located behind the podium of Hosack Hall could be added, will provide an ideal site for educational exhibit halls. Here would be the central point for utilizing the unexcelled facilities for graduate education which only the great medical institutions of the City of New York can jointly provide. And here also would be the center for indoctrinating the public with reliable scientific information for the purpose of correcting that mass of medical superstition and public ignorance which is the basis for much of the lag between great scientific discoveries and their application to the cure and the prevention of disease and of human suffering.

Although we possess the land, the erection of this much needed addition to the New York Academy of Medicine must unfortunately wait until some person with the means and the imagination appreciates the

importance of this great opportunity for the establishment of a new public service which can play so important a role in improving the quality of medical care in this City and throughout the Nation.

In opening this Nineteenth Fortnight on the subject of Tumors, I take pleasure in calling your attention to the fact that the establishment of the Graduate Fortnight was in large measure due to the influence and work of the late Dr. Ludwig Kast. It is, therefore, most appropriate that the opening lecture of the Fortnight should bear his name. It is now my pleasant duty to welcome the first speaker of the evening, the distinguished investigator who will deliver the Ludwig Kast Memorial Lecture, Dr. Peyton Rous of the Rockefeller Institute for Medical Research.

MEDICAL GENETICS AND PUBLIC HEALTH

The Twenty First Hermann M. Biggs Memorial Lecture

LAURENCE H. SNYDER

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THE field of public health has always been noted for its ability to put to practical use the basic discoveries of the various sciences which have had something to contribute to public welfare. With medicine as a core, public health has enlisted the aid and support of bacteriology, sanitary engineering, statistics, entomology, veterinary medicine, sociology and other pertinent disciplines. Following the early use of primitive measures of sanitation, the discovery of microbes opened a new and important phase of public health, leading to the control of many infectious diseases and the inspection and supervision of food and water supplies. More recently the activities in this field have widened to include such things as city planning, zoning, building of cheap transportation and recreational areas, provision of labor-saving devices and safety measures, and the general improvement of economic conditions.

These things, which have done so much for human progress, have been almost entirely aimed at the control of unfavorable conditions of the environment. Today most of these conditions are well under control, or at least could be if enough people wanted them controlled. There remain, however, a number of stumbling blocks to human health, the basic cause of which is genetic. As the infectious and nutritional diseases are conquered one by one, the genetic anomalies and diatheses become of greater relative importance. And just as the medical bacteriologist pointed the way to the control of infectious diseases, and the biochemist to the regulation of nutritional disorders, so the medical geneticist now holds out hope for the understanding, and thus the eventual control, of the genetic dyscrasias.

From the basic study of the principles of heredity there is emerging a new science, medical genetics, which applies these principles specifi-

cally to man. From careful research in the laboratory, in hospitals, and in homes and communities, a large amount of exact information has been gathered concerning the part that genetic variability plays in the production of human traits. Just as public health measures have depended for their success not only upon the training of specialists in the field, but also upon the education of the public, so also the newest handmaiden of public health, medical genetics, is developing both specialized and public interest. So important has our knowledge of human heredity become that courses in medical genetics are becoming standard units of the medical curriculum. Popular interest has dictated the appearance of books and magazine articles on human inheritance, and public lectures such as this one are being presented under a wide variety of auspices.

The precision of our knowledge has now reached the point where definite practical applications are available and in use. These include first, prevention, that is, the instituting of preventive measures against certain diseases and abnormalities, on the basis of specific genetic backgrounds; second, diagnosis, on the basis of genetic data, of conditions difficult to identify by other means; third, genetic prognosis, that is, the furnishing of genetic advice in prospective marriages and prospective families; and fourth, the determination of non-paternity and other medico-legal and medical problems, on the basis of the various blood agglutinogens.

Let us first consider prevention. Of all the applications of medical genetics, the one potentially most valuable is in the field of preventive medicine. It is becoming more and more feasible to prevent, in the relatives of persons with genetic conditons, the appearance of the abnormality or disease. The procedure is to examine the relatives of an affected patient by means of suitable laboratory tests, in search of the early pre-clinical or laboratory signs of the trait. When these are discovered, preventive measures are instituted.

Let me cite some examples from my own experience. At the Ohio State University I work in close association with the men in the departments of medicine and surgery. One of the most brilliant and certain applications of genetic facts to prevention has received much of its impetus from my colleagues in these departments, Doctors Doan and Curtis. I refer to the prophylactic removal of the spleen in congenital hemolytic icterus. In this disease the clinical manifestations are jaundice and marked anemia, sometimes developing as an acute fatal hemoclastic

crisis if permitted to remain untreated. The condition is the result of a dominant hereditary factor, but the clinical symptoms are not always expressed in those who inherit the factor. One or another of the laboratory stigmata is, however, always present if appropriate laboratory examinations are made. These signs include a relatively high reticulocytosis for the degree of anemia, microspherocytosis (rarely macrocytosis), increased fragility in hypotonic solutions of sodium chloride, increased icterus index, and enlarged spleen.

Where one or a combination of these signs is found in a relative of a patient with clinical activity, the spleen should be removed in the potential patient as a prophylactic measure. When it is remembered that such ordinarily minor events as an infection or a broken bone, or physiologic pregnancy in the female, may precipitate a hemoclastic crisis capable of resulting in death, the value and even the urgency of preventive splenectomy are apparent.

In connection with my University duties I teach a course in medical genetics to the medical students. It is my custom at the appropriate point in the course to have presented to the class a family in which hemolytic icterus exists. Recently I called Dr. Doan and asked if he could provide a case on a designated date. He assured me that there would undoubtedly be a case in the hospital at that time.

About a year previously, a man had been operated on for hemolytic icterus, and as is our custom, his children had been called in and examined. Two of his four sons showed the early laboratory signs of the inherited trait, and were advised to have their spleens removed as a prophylactic measure. One agreed, and his spleen was successfully removed; the other refused.

The day before my class period, Dr. Doan called and said that a boy with severe hemolytic icterus in hemoclastic crisis was being sent into the hospital, and would probably serve for presentation the next day. When the hour for the class arrived, however, Dr. Doan appeared without the patient. It had been the boy who a year earlier had refused preventive splenectomy. He arrived in extremis and lived just long enough to say, "I guess I waited too long to have my spleen removed." And he had. He could have been saved by elective prophylactic surgery on purely genetic grounds.

Another example of the genetic application of preventive measures is furnished by an anomaly known as xanthoma tuberosum. It is a stor-

age disease, a lipoidosis. Like hemolytic icterus, it has both clinical symptoms and pre-clinical laboratory signs. The visible symptoms are characteristic nodules and tumors of the tendons and joints. The laboratory signs consist of increases in the blood cholesterol and cholesterol esters. The increases may be as much as to reach 1500 mg. per cent., as compared with a normal blood cholesterol of 150-300 mg. per cent. The condition may progress to cardiovascular involvement and sudden death.

Since the hypercholesteremia is transmitted on the basis of a dominant hereditary factor, and since this may be detected by appropriate laboratory tests long before the appearance of visible tumors or nodules, it may profitably be searched for in the relatives of patients with clinical manifestations. Where found, preventive dietary and other appropriate measures may be instituted, thus helping to preclude heart involvement and premature death.

These are just two examples of many that could be cited. It might be argued by the uninitiated that such preventive measures could be invoked without any knowledge of genetics, and so they could, were it possible to examine everyone in the world for every potential disease and anomaly that he might have. Obviously this is not feasible, so that it becomes imperative to do the feasible thing, which is to search for laboratory and pre-clinical stigmata in the places where they are most likely to be found, namely, in the relatives of those patients who have clinically manifested genetic conditions.

Instances like those described, involving dominant genes, provide the most striking opportunities for the application of preventive measures on genetic grounds, since the incidence of affected relatives in cases of dominant heredity is high. A dominant gene is one which produces its effect whether it is present upon both or upon only one of the chromosomes of the pair concerned. A recessive gene, on the other hand, is one which must be present upon both chromosomes of the pair in order to produce its effect. Genes occur in alternative pairs, the two members of a pair being called *alleles*. Obviously if one allele of the pair is dominant, the other must be recessive. Dominant genes are usually symbolized by capital letters, their recessive alleles by the corresponding lower case letters. Thus we may represent the dominant gene resulting in hemolytic icterus by *I*, and its recessive allele for normal activity of the spleen and hematopoietic system by *i*. Then *II* and *Ii* will be the

genotypes (genetic compositions) of individuals with hemolytic icterus, and *ii* will represent the genotype of unaffected individuals. Persons of the genotype *II* are said to be *homozygous* for the gene *I*, while those of the formula *Ii* are called *heterozygous*. These two types of individuals can not be told apart by inspection, but may sometimes be distinguished by the types of offspring they produce.

Since hemolytic icterus is relatively rare, affected persons will usually be the offspring of one affected parent and one unaffected parent, and thus heterozygous *Ii*. Such persons will transmit the gene *I* to half their offspring, who, because of the dominance of *I*, will be potential sufferers. Similarly half the brothers and sisters of an affected patient will be expected to have the gene, and thus one or another of the stigmata.

Because hemolytic icterus is rare, we have not actually seen the homozygous condition, and can only assume that it would be the same as the heterozygous condition. Such a situation is the usual one. If a mating between two persons with hemolytic icterus should occur, we would have the possibility of observing an offspring with a double dose of the gene, one gene for icterus being inherited from each parent. Such a situation might conceivably result in a more severe form of the disease, or even in a lethal form. In our laboratory we have recently showed that multiple telangiectasia, which was long thought to be due to a simple dominant gene, is actually so severe as to be lethal when it occurs in the homozygous form. Similar situations obtain in one form of brachydactyly, in Pelger's anomaly, in sebaceous cysts and possibly in spina bifida.

The fact that not all persons who inherit the gene *I* show marked clinical symptoms of hemolytic icterus is an example of one of the basic physiological principles of genes, a principle known as *expressivity*. Some genes have constant expressivity, regularly producing the same degree of manifestation of the character. Other genes have variable expressivity, resulting in different manifestations of the trait from person to person.

Through researches subsidized by the National Research Council Committee on Human Heredity, of which I am chairman, Lennox and his coworkers[1] have shown that the dominant gene for epilepsy has variable expressivity. The basic expression of the gene is an abnormal brain wave as recorded by the electroencephalograph. This abnormal recording is known as *cerebral dysrhythmia*. It is the result of a dominant gene, and may be present with no clinical symptoms, or it may

develop into clinical epilepsy. Only about one person in twenty who inherits the gene and thus has cerebral dysrhythmia will actually develop clinical manifestations.

It is obviously important to learn the underlying causes of variable expressivity, so as to limit the expressions of genes as far as possible to innocuous effects. In some cases the variability is due to epistatic and other supplementary genes, in other cases to environmental causes such as trauma and irritation. There is unlimited opportunity for research in this direction.

Other examples of variable expressivity occur in pernicious anemia, where the achlorhydria may long precede the clinical symptoms; in allergy, where the expression may run the gamut of "hay fever," asthma, urticarial rash, eczema or angioneurotic edema; in neurofibromatosis, where the gene may result in tumors, café-au-lait spots, hemorrhage into a pachydermatococele, fibroma molluscum, plexiform neuroma, or elephantiasis neuromatosa; and many others. Knowledge of the variable expressions of genes is of value in setting up preventive and prophylactic measures, and may be of considerable importance in the next practical application to be discussed, that of diagnosis.

It is becoming more and more apparent that the alert physician will find occasional opportunities to make an otherwise difficult diagnosis by taking into account the family history of the patient. Let me again cite specific examples. My colleague, Dr. Macklin,[2] has recorded a number of instructive instances. In one case a man was admitted to the hospital, having lost considerable blood by hematemesis. The diagnosis appeared to lie between gastric ulcer, cirrhosis of the liver with esophageal varices, and Banti's disease. The appropriate laboratory tests were undertaken, but it happened that the next day one of the attending physicians recalled that the man's father had telangiectasia of a mild type, with typical spider-webbing of the capillaries of the nasal mucous membrane. Since telangiectasia is inherited on the basis of a dominant factor, it occurred to the doctor that perhaps all the patient had was a telangiectatic spot in the gastric mucosa. He explored, found a large telangiectatic focus, and excised it. The symptoms promptly disappeared, and there was no later recurrence of hemorrhage. Employment of available genetic data led to correct diagnosis and hence to proper therapy.

Again, a man had a corn on his foot which had ulcerated. Various

physicians whom he consulted were unable to give him any relief. One evening he made a social call upon a distinguished neurologist who happened to be a personal friend, and in the course of the evening hesitatingly mentioned this corn which would not get better, apologizing for bringing such a small matter to the attention of a specialist. To the man's amusement the neurologist asked for an X-ray of his lumbar spine. He did this because he had formerly treated the man's two brothers for marked trophic lesions which were the result of spina bifida. Sure enough, in this patient an occult spina bifida was found, and was shown to be the cause of the ulceration.

Not only may diagnoses sometimes be made more readily through the use of genetic backgrounds, but they may often be made earlier than would otherwise be possible. A man 54 years of age was operated on for well developed gastric carcinoma on the lesser curvature, one inch from the pylorus. His 52 year old brother, though having no symptoms, was disturbed by the presence of cancer in the family. The physician suggested that the appropriate tests be run on the brother. They were made, and an identical gastric cancer was found to be developing, one inch from the pylorus. Soon the brothers were in adjoining hospital beds, but the operation on the second brother was performed much earlier than would have been otherwise possible.

The third practical application of medical genetics to public health is our increasing ability to give accurate genetic advice to families. As a result of college courses in genetics, and of popular books and magazine articles on heredity, the well-read layman is rapidly learning that it is possible to get information about the possibility of the appearance in his children of a trait that has previously occurred in the family. Parents and prospective parents are rightfully concerned about these things. Sometimes the question concerns a wanted character such as blonde hair or musical ability. More often it involves an unwanted trait such as club foot, achondroplasia, or mental deficiency.

Before attempting to answer such a question the physician must ascertain several important facts. He must first accurately identify the trait, since minor variations may represent different genetic factors involved. The ease of identification varies: club foot is readily recognized, while border-line mental deficiency may be difficult of analysis.

When the trait is accurately identified or diagnosed, the literature on human and medical genetics must be searched for recorded instances of

the hereditary mechanism involved. Particular care must be taken to note what variations in the expression of the trait have been recorded within families, what the ages of onset have been, and with what regularity the character may have appeared within families.

It is then necessary to chart the family history of the person seeking advice, and to compare his pedigree with those recorded in the literature or in the files of the physician himself, noting similarities and differences in symptoms, age of onset, and type of transmission.

Finally the possible relations of the anomaly or disease to the environment must be evaluated, and the probable environment in which the trait will develop if it appears in this family must be specified.

With all the above facts in hand it is frequently possible to make a reasonable prognosis. Let me again draw some instances from personal experience.

Within the past year I have been consulted by two families on the question of peroneal atrophy. In one case the father suffered from the disability and wished to know the possibility of its appearance in his children. He had noticed beginning lameness in his late twenties, and at forty he showed pes cavus and atrophy of the hands. He was an only child, and he remembered his mother as being moderately crippled. The late onset and moderate involvement are characteristic of the dominant form, and it was thus possible to predict that about half his children of both sexes would show the trait.

In the other instance the parents were unaffected, but their oldest child, a boy of twelve, was severely crippled. He had begun to have trouble walking at about five years of age, and the atrophy had developed rapidly. Their other children were two girls, aged seven and two, respectively. The parents wanted to know the chances of the two girls developing the atrophy, and whether or not any of these children could transmit the trait.

The onset during the first decade and the rapid crippling are characteristic of the recessive form of peroneal atrophy. In the case of recessive traits, it will be recalled, the gene must be present on both chromosomes of the pair in order that the trait be expressed. This means that it must have been inherited from both parents. In this case, since both parents were unaffected, they must have been heterozygous. In rare recessive traits, it will be unusual to find both parents heterozygous by chance. The situation is much more likely to occur, however, when the

parents are related, since, if one is heterozygous for a trait, the other, being a relative, is likely to carry the same gene. In the family under discussion, inquiry revealed that the parents were first cousins.

It was thus possible to tell the parents that any child of theirs has one chance in four of becoming crippled. Moreover, the normal children have two chances in three of carrying the gene. Even if one of them carries the gene in heterozygous form, however, it will not result in affected children unless she marries a man who is likewise heterozygous.

The foregoing cases illustrate the fact that variations in onset and severity within a trait are often the result of different genic complexes. Conversely, the discovery of various genetic bases for what is apparently a single clinical entity can lead to important clinical distinctions which may even require different therapies. In devious ways is medical genetics making its importance felt in clinical medicine and public health.

Other examples of variations in onset and severity dependent upon different genes are to be found in epidermolysis bullosa and in retinitis pigmentosa.

Recently I was asked to advise a couple with three sons and two daughters. Two of the sons, aged nine and eleven, suffered from pseudohypertrophic muscular dystrophy. A brother of the mother had died of the disease at the age of fourteen. The parents were well aware of the hopeless prognosis for the two crippled boys, but wanted information on the chances of the reappearance of the trait if the normal boy and the two normal girls should marry.

The abnormality in this case is the result of a sex-linked gene, that is, a gene carried on the X-chromosome. Since the gene is recessive, it must be on both X-chromosomes of a woman to express itself, but due to the fact that the boys having this defect usually die before reproductive age, there is little or no chance for a girl to get the defective gene from her father. This type of dystrophy is therefore confined to boys. The chromosome complex of a male includes an X- and a Y- chromosome in place of two X-chromosomes in a female. The Y-chromosome carries no genes of this sex-linked type, so that if a boy inherits the gene for dystrophy on the X-chromosome from his mother, the Y-chromosome from his father will not contribute any gene to counteract or dominate over the defective gene, which can therefore express itself.

If we represent the gene for normal muscle development by *D*, and the gene for dystrophy by *d*, boys may be either of two genotypes, *DY*

(normal) and *dY* (crippled). Girls will ordinarily be one of two genotypes, *DD and Dd,* both unaffected. The genotype *dd* (dystrophic female) can obviously not occur as long as the crippled boys die before reaching reproductive age.

The defective gene is thus carried along in the population by some of the normal girls in the dystrophic families. In the family under discussion the parents were obviously *DY* (father) and *Dd* (mother). All the boys received the Y-chromosome from the father, but had an even chance of receiving *D* or *d* on the X-chromosome from the mother. The two crippled boys, of course, received *d* and were thus *dY*. The normal brother, who was fourteen years of age, obviously received *D* and was DY. It was thus possible to state definitely that he may marry with impunity, since he can not possibly transmit the gene.

The daughters, on the other hand, both received *D* on the X-chromosome from the father. Although they were only three and five years old, respectively, it is certain that they will be unaffected. However, they have an even chance that they carry the defective gene from the mother. Thus the chances that they may bear crippled sons are fifty-fifty, regardless of whom they marry.

Not long ago I was consulted by a young couple who had an infant son suffering from an affliction of the skin in which blebs and blisters appeared wherever the skin was subject to friction. The blisters occurred not only on the skin itself, but in the mouth, nose and throat. The child had no nails and practically no teeth, and was a mass of raw flesh. The diagnosis was made of epidermolysis bullosa dystrophica. The prognosis is bad. The parents were frantic, and demanded to know whether further children would show the defect.

This type of epidermolysis is known to be the result of still another kind of gene, an incompletely sex-linked gene. Such genes are located on the homologous regions of the X- and Y-chromosomes. These chromosomes are complex, and recent work by Koller[3] has shown that they consist of three portions, as follows. First, there is a region of the X-chromosome homologous with a corresponding region of the Y-chromosome, the two parts synapsing during meiosis and forming chiasmata. Second, there is a part of the X-chromosome not homologous with any part of the Y-chromosome; and third, there is a portion of the Y-chromosome not homologous with any portion of the X-chromosome. The non-homologous regions do not undergo synapsis during meiosis.

Genes are known to be located in each of these three regions, and all such genes will be in one way or another associated with sex in their inheritance. Those located on the non-homologous portion of the X-chromosome are called sex-linked, and will be inherited in the manner just described for pseudohypertrophic muscular dystrophy. Genes located on the non-homologous region of the Y-chromosome will be confined to men, and will produce their characteristics only in men. Such traits as ichthyosis hystrix gravior and keratoma dissipatum are of this nature.

Genes located on the homologous parts of the X- and Y-chromosomes are known as incompletely sex-linked genes, and their transmission is peculiar. About half the families in which the father carries the gene will contain more affected sons and unaffected daughters than would be expected in ordinary inheritance, while the other half will contain more affected daughters and unaffected sons than would be expected. The extent of the discrepancy will depend on the precise location of the gene on the chromosome. The location can be accurately determined by modern genetic methods.

The gene for epidermolysis bullosa of the recessive type is, then, incompletely sex-linked, and located about 20 units distant from the junction of the homologous and non-homologous portions of the sex chromosomes. Since the affected child in the family was a boy, this probably represents a non-crossover, and other affected children in the family will probably be boys. Specifically, another boy in this family would have two chances in five of being affected, whereas a girl would have but one chance in ten of showing the affliction.

The foregoing examples of genetic prognosis are all instances in which sufficient information on the mode of inheritance of the abnormality was available to make accurate predictions possible. Unfortunately, complete genetic data are not equally at hand in all inherent anomalies, and such explicit information can not always be given. There is crying need for more and more research along these lines.

The fourth practical application of medical genetics includes the medico-legal and other medical outcomes of our knowledge of the inheritance of the human blood agglutinogens. It is like carrying coals to Newcastle to speak of the blood groups to a New York audience. This is the place where Dr. Landsteiner, the discoverer of the blood groups, did so much of his work; where he and Dr. Levine worked out antigens

M and N; and where Dr. Wiener is even now continuing his remarkable work on the Rh factors. Nevertheless, any discussion of medical genetics and public health would be very incomplete without at least a reference to the subject.

More than twenty years ago I spoke in New York on the inheritance of the blood groups. At that time we knew of four groups, and I thought I had a good deal to say about them. Today we deal with 3200 groups, and the number will probably soon exceed 8000 by virtue of several new antigens which are even now in the process of description.

It will be recalled, then, that in the early days of this century Landsteiner showed that when the erythrocytes of one person were mixed with the serum of another person, agglutination might occur. The reaction took place only in certain mixtures of cells and sera. It was obviously an antigen-antibody reaction, the antigen being located in the erythrocytes, the antibody in the serum. Further work revealed the fact that there were really two antigens occurring in human erythrocytes. These were named A and B. As a result it was possible to distinguish four sorts of individuals: those containing antigen A in their cells (hence spoken of as belonging to group A), those having antigen B (group B), those having both antigens (group AB), and those possessing neither antigen (group O).

A reciprocal relationship exists between antigens A and B and their corresponding antibodies, since each person has either antigen A or the antibody against A, and either antigen B or the antibody against B. Thus there occur in various human bloods natural or "normal" antibodies against A and B.

The most obvious application of this discovery was to blood transfusion, since it would be unwise to transfuse red cells into a person whose plasma would immediately clump the cells. Before any transfusion of whole blood or erythrocytes, the blood groups of donor and recipient must be determined, so that compatible blood may be given.

We were immediately intrigued by the fact that here was a means of distinguishing four kinds of people, and in our laboratory and those of other investigators, researches were quickly undertaken to determine how the blood groups were inherited. Studies of large numbers of families have disclosed the fact that antigen A is inherited on the basis of a dominant gene. Antigen B is the result of another dominant gene, an allele of the first, and a third allele in the series results in no antigen at

all. Consequently antigen A never occurs in a child's blood unless it occurred in the blood of at least one of the parents. Similarly, antigen B never appears in a child's blood unless it was present in the blood of at least one of the parents.

Although these discoveries seemed at first only of academic interest, they proved soon to be of practical importance as well. Cases of disputed paternity, for example, may be settled from data such as these. If a child, for instance, is of group A, and the mother is of group O, then we know that the antigen A in the child must have come from the father. If the alleged father should be of group B or of group O, we can state definitely that he is not the true father of the child.

Following the first world war the intensive study of blood grouping phenomena was undertaken on a large scale. One of the outcomes of these researches was the demonstration that antigen A occurs in several detectable subtypes, now named A^1, A^2 and A^3. It is thus possible to classify people into eight different groups, namely O, A^1 A^2 A^3, B, A^1B, A^2B, and A^3B.

Another outcome of blood grouping research was the demonstration that antigens A and B exist in two different chemical forms: water-soluble and alcohol-soluble. Thus individuals of groups A, B and AB may produce water-soluble antigens, in which the antigens are found not only in the cells but in the body fluids such as the saliva, milk, tears and urine. On the other hand, they may produce the antigens in alcohol-soluble form, in which case they will be restricted to the cells.

Those persons having water-soluble antigens have been named "secretors," while those whose antigens are not soluble in water are called "non-secretors." By means of special anti-O sera, even individuals of group O can be classified into these two groups.

The "secreting" ability is the result of a dominant factor, the "non-secreting" propensity being due to its recessive allele. Thus these factors may be added to the armamentarium for medico-legal use. Also they double the number of recognizable blood groups. Since any one of the eight A-B groups may be either a secretor or a non-secretor, there are 8 x 2, or 16 groups recognizable in this way.

The discovery of antigens A and B resulted from the presence in human sera of normal antibodies against them. On the assumption that there might be in human erythrocytes other antigens for which no normal antibodies existed, Landsteiner and Levine injected human cells into

rabbits. When the resulting immune sera were exhausted with appropriate human erythrocytes, the sera still selectively agglutinated other samples of human red cells. It was apparent that the rabbits had produced a specific antibody against a human agglutinogen not previously recognized. As a matter of fact, several agglutinogens were found by this technique.

Two of the new agglutinogens were named M and N. They proved to be related in such a way that a person might have M in his cells (type M), or N (type N), or both (type MN). No one lacking both M and N has been found. Through genetic studies it has been demonstrated in our laboratory and others that these antigens, like A and B, are the result of dominant genes, and consequently never appear in a child's blood unless present in the blood of at least one of the parents.[4] Moreover antigen N, like antigen A, can be subdivided into identifiable types. We recognize N^1 and N^2, so that there are five types in the M-N series, namely M, N^1, N^2, MN^1 and MN^2. Since any one of these five could be any one of the sixteen AB groups, there are 5 x 16, or 80 different groups detectable in these two series.

In addition to lacking normal antibodies, M and N have proved to be only very weakly antigenic to human beings. They are thus unimportant in blood transfusion, even in multiple transfusions. They can be used, however, as additional criteria in cases of disputed paternity.

In the course of the injection experiments carried out by Landsteiner and Levine, still another antigen lacking normal antibodies was found. It was less satisfactory to use than antigens M and N, since potent sera were difficult to obtain and standardize, and the reactions were weak and variable. The antigen was named P, and later work has resulted in more satisfactory means of detection. For one thing, certain animals have been found to be good sources of normal anti-P serum, particularly pigs.

Genetic studies reveal that antigen P, like the others mentioned, is the result of a dominant factor. Moreover it likewise occurs in two detectable subtypes, P^1 and P^2, so that with the appropriate antisera four kinds of persons can be distinguished, namely P^1, P^2, P^1P^2 and P-.

In the combined A-B, M-N and S series there were 80 different classifications of human blood. Since the P factors are independent of the others, any one of the 80 could be any one of the 4 types in the P series, thus making altogeher 80 x 4, or 320 different groups.

Continued attempts at discovering more antigens by injection of

human blood into animals gave disappointing results. Landsteiner and Wiener therefore approached the problem from a different angle. They injected blood from the monkey, *Macacus rhesus*, into rabbits. The immunized rabbit serum was found to agglutinate human cells selectively, thus identifying still another human agglutinogen which proved to be independent of all those previously studied. Using the first two letters of rhesus, the antigen was named Rh. Eighty-five per cent of white Americans proved to have the new antigen, and these persons are spoken of as Rh+. The other fifteen per cent, lacking the antigen, are called Rh–.

Genetic studies of the new antigen revealed the fact that it, too, is inherited on the basis of a dominant gene, and may therefore be used with the other antigens in medico-legal applications.

There are apparently no normal antibodies against antigen Rh in human plasmas. In this regard the situation is similar to that in antigens M and N. There is a difference, however, in regard to antigenicity, since Rh is antigenic to man. This fact leads to several extremely important clinical applications.

In blood transfusions it is essential to transfuse only Rh– blood into an Rh– person, since repeated injections of Rh+ blood may result in immunization of the recipient with hemolytic reactions of increasing severity.[5]

Not only is the Rh agglutinogen antigenic to man, but it may pass from the circulation of an embryo through the placenta into the mother's circulation, and immunize the mother if she is Rh negative. This fact led to the discovery of the cause of erythroblastosis, which had long been known to run in families, but which had never fitted into any clear genetic picture.

Even before the discovery by Landsteiner and Wiener of the Rh antigen, Levine and Stetson[6] postulated such a factor capable of immunizing a mother. They found an atypical agglutinin in the blood of the mother of a macerated fetus. When the Rh factor was announced the following year, it proved to be the immunizing agent postulated by Levine and Stetson. In 1941 Levine, Katzin and Burnham[7] demonstrated that the Rh antigen is indeed the primary cause of erythroblastosis, accounting for more than 90 per cent of the cases. Recent work of Wiener and his coworkers has established the fact that the other 10 per cent are also due to immunization reactions, either the result of the production

of univalent Rh antibodies instead of the usual bivalent agglutinins, or in occasional cases the result of antigens A and B.

In nearly all cases of erythroblastosis the mother is Rh–, the fetus Rh+. The antigen in the fetus was, of course, inherited from the father, and some of it has passed through the placenta into the circulation of the mother, immunizing the mother. The maternal immune antibody, which can be demonstrated in the mothers of erythroblastotic infants, has then passed back into the fetus, damaging the erythrocytes. The result is hemolytic jaundice or fetal hydrops or macerated fetus, the well recognized symptoms of erythroblastosis. While the agglutination of red cells is a demonstrable test tube reaction, the end result in the fetal circulation is most probably hemolysis.

As a rule the first Rh+ pregnancy of an Rh– mother serves merely to set up the immunization, while a second or later Rh+ embryo stimulates the further rapid production of antibodies, and is itself affected. Occasionally, however, a woman produces antibodies so quickly and strongly that even the first Rh+ embryo may be affected. We have some evidence in our laboratory that these affected first-born show gross abnormalities, including spina bifida. Within the past year we have seen several such cases, and these will shortly be published.

Of course, if an Rh–woman has received a transfusion of Rh+ blood previous to her first pregnancy, she may already have been immunized, and the first Rh+ fetus she carries may then be affected in the usual manner. On the other hand, some women appear to produce antibodies so slowly that several Rh+ fetuses are required before one shows the effect of the immunization.

Although the original source of anti-Rh serum was immunized rabbits, and later immunized guinea-pigs, it was soon apparent that the serum from mothers of erythroblastotic infants was the best source of test antibodies. Nowadays such mothers furnish practically all the available test sera. The study of such sera has resulted in the discovery of several types of anti-Rh antibodies, making possible the identification of corresponding new Rh antigens, and the classification of still more kinds of persons.

Not long after the discovery of the original Rh agglutinin, Wiener[8] found a human immune serum which agglutinated only 70 per cent of human bloods instead of 85 per cent. The new agglutinin identified another Rh antigen, similar to the first. The original antigen is now called

TABLE I

Types	*Observed Frequency*	*Genotypes*	*Theoretical Frequency*	*Anti Rh° .85*	*Anti Rh' .70*	*Anti Rh" .32*	*(Anti Hr°) .63*	*Anti Hr' .80*	*Anti Hr" .97*
Rh°	.024	*Rh° Rh°*	.001024	+	—	—	—	+	+
		Rh° rh	.02336	+	—	—	+	+	+
Rh° '	.543	*Rh° ' Rh° '*	.187489	+	+	—	—	—	+
		Rh° ' Rh'	.011258	+	+	—	+	—	+
		Rh° ' Rh°	.027712	+	+	—	—	+	+
		Rh° ' rh	.316084	+	+	—	+	+	+
		Rh° Rh'	.000832	+	+	—	+	+	+
Rh° "	.137	*Rh° " Rh° "*	.021025	+	—	+	—	+	—
		Rh° " Rh"	.00087	+	—	+	+	+	—
		Rh° " Rh°	.00928	+	—	+	—	+	+
		Rh° " rh	.10585	+	—	+	+	+	+
		Rh° Rh"	.000192	+	—	+	+	+	+
Rh° ' "	.132	*Rh° ' Rh° "*	.12557	+	+	+	—	+	+
		Rh° ' Rh"	.002598	+	+	+	+	+	+
		Rh° " Rh'	.00377	+	+	+	+	+	+
Rh'	.005	*Rh' Rh'*	.000169	—	+	—	+	—	+
		Rh' rh	.00499	—	+	—	+	+	+
Rh"	.002	*Rh" Rh"*	.000009	—	—	+	+	+	—
		Rh" rh	.00219	—	—	+	+	+	+
Rh' "	.000	*Rh' Rh"*	.000078	—	+	+	+	+	+
Rh—	.133	*rh rh*	.133225	—	—	—	+	+	+

The genetic basis of the Rh-Hr blood types. The theoretical genotype frequencies were derived in my laboratory from the proportions of the Rh types as recorded by Wiener. It should be noted that anti Hr^s has been postulated but not yet described.

Rh° (or Rh_o) and the new one is known as Rh'. Soon afterward Levine[9] described an immune serum which contained antibodies against both antigens, and agglutinated about 87 per cent of human bloods.

Still later Wiener[8] described a third kind of human immune serum which contained a new agglutinin, related to the other two, but reacting with only 32 per cent of human bloods. The new antigen indentified by this antibody has been named Rh". Individual persons may have any one of these antigens in their erythrocytes, or any combination of them, or none at all. Thus with the appropriate antisera anyone may be placed

in one of eight Rh types, as follows: Rh°, Rh′, Rh″, Rh°′, Rh°″, Rh′″, Rh°′″ and Rh-. The last type is Rh negative, the others are all Rh positive, for one or more of the Rh antigens.

Based on the blood groups in the A-B, M-N, S and P series, we have, it will be recalled, 320 types. Since any one of these 320 could be any one of the eight Rh types, we can now distinguish 8 x 320, or 2560 blood groups altogether.

Most recently it has been observed that corresponding to each Rh factor there is a reciprocally related antigen which has been named Hr.[10] Hr is related to Rh in the same way that M is to N, so that a person homozygous for any Rh gene is negative for the corresponding Hr antigen, and vice versa. Corresponding to the three antigens Rh°, Rh′ and Rh″, three Hr factors, Hr°, Hr′ and Hr″ are postulated. Hr′ and Hr″ have already been described; Hr° will doubtless soon be discovered and delineated.

The addition of the Hr antigens to the list makes it possible to break each of the eight Rh types into further subdivisions (Table I). Using anti-Hr′ serum, for example, we may now classify Rh°′ blood into positive for Rh°′ but negative for Hr′, and positive for Rh°′ and positive for Hr′. Interestingly enough, in most cases this difference will distinguish homozygous individuals from heterozygous individuals, as may be seen from the table, and is thus of importance in genetic prognosis in families in which erythroblastosis has occurred.

Antisera against Hr′ are now available, and make it possible to readily distinguish ten Rh blood types instead of eight. Going back to the 320 types classifiable on the basis of A, B, M, N, S and P, and realizing that any of the 320 could be any one of the ten Rh-Hr types, we have now 3200 different blood groups. When antisera against Hr° and Hr″ become available in quantity, it will be possible to distinguish 27 Rh-Hr types, and thus 27 x 320, or 8640 blood groups altogether.

The different genes involved in the production of these diverse antigens occur in varying frequencies from population to population, and herein lies another whole field of research. In any population some of the alleles will be fairly common, others rather rare. Nevertheless, it would be possible for me to take a drop of blood from each one of you in the audience tonight, and with the aid of the proper sera, to place each one of you in one of these thousands of blood groups. It would be surprising if any two of you were to fall into the same group. Then

five years later I could return here, gather you together, take another drop of blood from each of you, and, without knowing the source of the samples of blood, assign each sample to the proper person by referring to my previous list, except, of course, for such duplications of blood group as might exist among you.

Returning to erythroblastosis, the question arises as to how often by chance an Rh– woman will marry an Rh+ man and produce an Rh+ child who might thus be affected. This problem, like all the problems involved in the Rh types, is one of medical genetics, and can be solved only by medical genetic methods. Its solution has led to some remarkable new concepts of Rh immunization. Without going into the mathematical methods of gene-frequency analysis, let me say only that we would expect in a population such as ours that 23.8 per cent of all children born will have one or another Rh antigen which the mother does not have.

If all such cases are potentially erythroblastotic, we should expect the incidence of erythroblastosis to be 23.8 per cent. However, the frequency of clinically diagnosed cases has never approached this figure. The recorded incidence is about one in 200 births, or about one half of one per cent. Obviously the difference between 23.8 per cent and one half of one per cent is a pretty big discrepancy, and it is of importance to explain it.

First of all, it has been observed that of the three Rh antigens, only Rh° is of any great importance in producing symptoms. There have been a very few cases reported of effects due to immunization with Rh′ or Rh″, but the number is relatively insignificant. We may confine our attention, then, to Rh°. When we compute how often a child will be expected to have Rh° when the mother lacks it, we find that the answer is 8.5 per cent. This is much closer to the observed half of one per cent, but still far enough away to demand further investigation.

Next we recall that first-born children are seldom affected. In our American population about 31 per cent of children are first-born. Eliminating these from our calculations, we would expect 6 per cent of children to have Rh°, to be born of mothers lacking Rh°, and to be second- or later-born in the family. This further closes the gap between the expected and the observed incidence of symptoms due to Rh immunization, but still leaves a discrepancy.

Looking further, we see that the cases of erythroblastosis are not

distributed randomly among the Rh– mothers, but are grouped into specific families. This suggests that the Rh° antigen may permeate the placenta only in certain Rh– mothers, or that perhaps only certain Rh– women are capable of producing potent antibodies. It may be that both these things account for the fact that not as many cases of erythroblastosis are found as can potentially occur.

Another intriguing possibility suggests itself, and the exploration of this possibility has led to suggestive results. It is conceivable that in some instances where the antigen immunizes the mother, and the antibody in turn reaches the fetal circulation, that the effects on the fetus are different from those usually recognized as classical erythroblastosis.

In various laboratories, including our own, the search has been made for such manifestations.[11] The results indicate that the effects of Rh immunization are unimportant in the production of early abortions, and in the etiology of hemolytic icterus, sickle cell anemia, hydatiform mole, ectopic pregnancies, eclampsia and specific toxemia. In undifferentiated mental deficiency, however, positive results were obtained.

In 1944, Yannett and Lieberman[12] made an examination of the blood groups and types of the children in a school for the feebleminded, and of their mothers. They found too many Rh– mothers in the group, and too many Rh+ children of Rh– mothers. Analyzing the results it was found that of 109 feebleminded children, 53 were distributed among the specific types of mental deficiency such as Mongolian idiocy and spastic paraplegia. The distribution of the Rh factor was normal in these children and in their mothers. In the 56 children classified as undifferentiated mental deficiency, however, an abnormal distribution of the Rh factor appeared. There were too many Rh– mothers and too many Rh+ children from these Rh– mothers.

These results appeared to us so suggestive that we have been investigating the blood of the undifferentiated feebleminded at the Ohio Institute for the Feebleminded, and of their mothers (Snyder, Schonfeld and Offerman,[13] 1945). The results to date are as follows. Of 169 mothers of feebleminded children, 38 are Rh–, whereas only 21 or 22 would be expected. This difference is statistically highly significant. Of 171 feebleminded children, 27 are Rh+ from Rh– mothers, whereas we should expect only 14 or 15. This deviation is also highly significant when tested statistically.

It thus appears that the immune antibodies of the mother may pro-

duce effects on the brain tissue instead of the usual symptoms of erythroblastosis. The suggestion has been made that the immediate effect of red-cell destruction is anoxia, and that this lack of oxygen, if it occurs at a time when the brain of the embryo is in a critical stage of development, may very well cause permanent mental deficiency. As a tentative estimate of the incidence of this effect I suggest a half of one per cent.

Thus the gap between the calculated incidence of effects of Rh immunization and the observed incidence has been still further closed. It is not yet completely closed, however, and the search must continue for further, as yet unknown, manifestations. In our laboratory we have recently completed an analysis of a hundred cases of dementia praecox and their mothers. The distribution of the Rh factors agrees satisfactorily with expectation in these cases.

There is some evidence that incompatibility of A and B can cause mild symptoms in cases where the fetus has one of these antigens which is lacking in the mother. Mild jaundice of group A infants from group O mothers has been reported by Polayes[14] (1945). In these cases the titer of anti-A antibodies was found to be 1:700 as compared with an average of less than 1:200.

Another recent and important contribution to the rapidly developing Rh picture is the discovery by Wiener that immunization may result in either of two kinds of antibodies: bivalent, resulting in typical agglutination, or univalent, resulting, in the presence of conglutinin, in "conglutination." It is Wiener's belief that the type of manifestation of erythroblastosis depends upon which of these kinds of antibodies is produced. Since the type of antibody production may well be the result of a genetic factor, further intriguing problems are posed by this discovery.

Still another field for speculation is opened by the recent suggestion of Butts[15] that the malarial parasite may contain an Rh-like antigen which, through immunization, produces blackwater fever as a sequella of malaria in Rh negative persons.

Through these various examples of the growth and increasing importance of medical genetics I have tried to point out its place, shoulder to shoulder with the older sciences, as an ally of public health. Someone may ask, what about a program of eugenics as a part of public health measures? My answer is that this *is* eugenics. These things I have been describing to you form the essence of modern eugenics.

In the continuing struggle for the health and well being of all mankind, medical genetics stands ready to join those sciences which have already made so much progress, in the hope and belief that its contribution may likewise prove a worthy one.

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FIBROUS DYSPLASIA OF BONE*

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THE disorder which Doctor Lichtenstein and I[1, 2] designate as "fibrous dysplasia of bone" has, as its central and constant feature, a characteristic kind of skeletal lesion developing in the interior of affected bones. In any particular case, one, several, or many bones may be involved, and part or much of the interior is occupied by a tissue which is basically fibrous and gritty though it may also present other features, which will be brought out later. In some cases, the skeletal aberration constitutes the entire disorder, so far as one can tell. In other cases, the disorder is expressed as an association of the skeletal aberration with the presence of one or more non-elevated light yellow or yellow-brown areas of cutaneous pigmentation. Stauffer, Arbuckle, and Aegerter[3] have also described a case in which, in addition to extensive skeletal changes and a large, brownishly pigmented patch on the back, there were multiple congenital arteriovenous aneurysms in the left upper extremity and apparently also in the left lower.

However, the vast majority of the cases of fibrous dysplasia is constituted by those showing only the dysplastic skeletal changes (in one, several, or many bones) or such skeletal changes along with some abnormal cutaneous pigmentation. The small percentage of cases remaining can be held to represent the full-blown form of the disorder. In this form, specifically, the patient presents the skeletal changes (usually together with some abnormal pigmentation) and also shows, or has shown, premature skeletal maturation and precocious puberty, sometimes along with hyperthyroidism and even some other abnormalities.

It is these full-blown cases that are commonly denoted as instances of Albright's disease,[4, 5] though McCune and Bruch[6] called attention to them at the same time and then already mentioned, as did Albright, a number of cases previously reported in the literature under various titles. The case reported by McCune and Bruch represents one of the

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most carefully followed instances of the disorder, having been studied clinically by them over a period of about 6 years and then, at the time of the patient's death at the age of 12½ years, anatomically by Sternberg and Joseph[7] on the basis of a complete autopsy. In spite of their relatively small number, these cases bulk large in the literature, because their spectacular qualities make them attractive subjects for reporting.

We estimate that for every case of the florid type there are 20 or 30 cases of the type which we have emphasized—that is, cases in which the fibrodysplastic involvement of the skeleton is not associated even with any striking cutaneous pigmentation, apparently not with any skeletal precocity, and certainly not with sexual precocity and/or hyperthyroidism. Various observers, including Uehlinger,[8] have confirmed the identity of the skeletal lesions in the latter type with the skeletal lesions in the cases called cases of Albright's disease. Indeed, as stated by Falconer, Cope, and Robb-Smith:[9] "Albright's disease must be regarded as an association of cutaneous pigmentation and endocrine disturbances—of which the most striking is precocious puberty in girls—with a characteristic skeletal disorder [fibrous dysplasia of bone] which may occur by itself." However, though actually denoting only the dysplastic skeletal changes common to all cases, the term "fibrous dysplasia of bone" as applied to the disease complex as a whole has the advantage that it emphasizes the central and constant feature of the disease complex and can be qualified in accordance with the special features of individual cases.

We know nothing of the etiology of the condition, but the systemic character of the disease complex as a whole strongly suggests that it has its basis in some deep-rooted developmental defect, though it does not show any familial or hereditary factor. In a sense, the individual bone lesion may be conceived as a hamartoma—that is, a tumor-like malformation resulting from flaws of development and characterized by defects of tissue combination.

Clinical and Anatomic Aspects of the Disorder

No useful purpose would be served by repeating here the details on the disorder as a whole which were given in the article of 1942 by Lichtenstein and the present writer.[2] The reader is also referred in this connection to the excellent review article by Falconer, Cope, and Robb-Smith.[9] We shall limit ourselves here to orienting remarks on the clinical

and anatomic features of the disorder as a whole, and consider in their appropriate connections some features which we have not stressed before.

Fibrous dysplasia of bone is by no means a rare disorder; our own experience with it now includes at least 30 cases. The disease is definitely more common in females than in males. Most of the cases come to light during childhood or adolescence, from some complaint (pain, deformity, fracture, etc.) referable to changes in some bone or bone part. The florid cases in females usually come to light quite early in childhood, on account of precocious puberty, though abnormal cutaneous pigmentation and even skeletal difficulties may have been present previously. On the other hand, in clinically mild cases in which the disease is limited to involvement of one bone or at most a few bones, the condition may remain clinically silent even until late in adult life and even then be discovered only accidentally.

Topography and Anatomy of the Dysplastic Skeletal Lesions: As noted, in any particular case, one, several, or many bones may be affected, and, strikingly, in the cases showing multiple bone involvement, this tends to be exclusively or at least predominantly, on one side of the body. Furthermore, within a given affected tubular bone, the disease is nearly always limited to the shaft. When one bone is involved, this is often a rib, a femur or tibia, or a facial bone (particularly a jaw bone) but may be almost any bone. When a number of bones are involved, these are quite likely to be bones of one limb bud—especially a lower one. Typically, then, one finds the femur, tibia, and fibula affected, and perhaps also some bones of the foot and part of the innominate bone on the same side. On the other hand, there are cases in which, though only a limited number of bones are involved, these are exclusively trunk bones—for instance several ribs (not necessarily on one side), alone or with several vertebrae.

These cases in which a limited number of bones are affected merge without sharp delimitation into those cases in which the skeletal involvement can be said to be moderately or frankly severe. Thus one sees cases in which, while the lesions are located particularly in bones of the upper and lower limb on one side of the body, there are also at least some in limb bones on the other side, along with lesions of some skull bones, ribs, and pelvic bones, especially on the side on which the limb bones are more extensively affected. All in all, the tendency toward

restriction of involvement to the bones of one limb bud, or at least more heavy involvement of the bones on one side of the body when bones of the thorax and skull and bones of more than one limb bud are implicated represents an important clinical and roentgenographic hallmark of the disease.

An affected bone or bone area may retain its original contour. Often, however, the contour is distended, at least in part, because of erosion of the cortex from within and the yielding of the newly formed cortex to internal pressure. In either case, as noted, the interior of the affected bone or bone area is found to be filled mainly by an evenly whitish or reddishly speckled rubbery and compressible tissue. Fundamentally, this is fibrous connective tissue. It may be gritty throughout from the presence everywhere in it of newly formed trabeculae of immature bone. Or, instead, it may show some smaller or larger non-gritty, highly collagenous areas in which few if any bone trabeculae are to be seen. In some lesions, islands of hyaline cartilage may also be present within the fibrous connective tissue. Furthermore, in an occasional lesion, focal degeneration of, or hemorrhage into, this tissue may have led to the formation of smaller or larger secondary cysts. In areas of organizing hemorrhage, a few scattered or clumped multinuclear giant cells may be observed. In an occasional lesion one may find some nests of foam cells within the fibrous tissue. These may be seen in connection with hemorrhage or focal degeneration of the connective tissue cells and hardly represent a noteworthy feature of the condition except in so far as they may lead to a mistaken diagnosis of lipogranulomatosis (Schüller-Christian's disease). Finally, in some areas or some lesions, so much new bone may form in the connective-tissue substratum that the latter sinks into the background and the replacement tissue has a definitely osseous character.

Roentgenographic Appearance of the Dysplastic Skeletal Lesions: The roentgenographic picture presented by an affected bone or bone area is determined in its essentials by the character of the replacement tissue in the bone interior and by the effects of this tissue on the neighboring cortical bone. Thus this picture varies from one affected bone area to another in accordance with the degree to which the bone contour has been expanded by erosion of the cortex, ridges have developed upon the inner aspect of the newly formed cortex, new bone has been formed in the connective-tissue substratum, and this tissue has under-

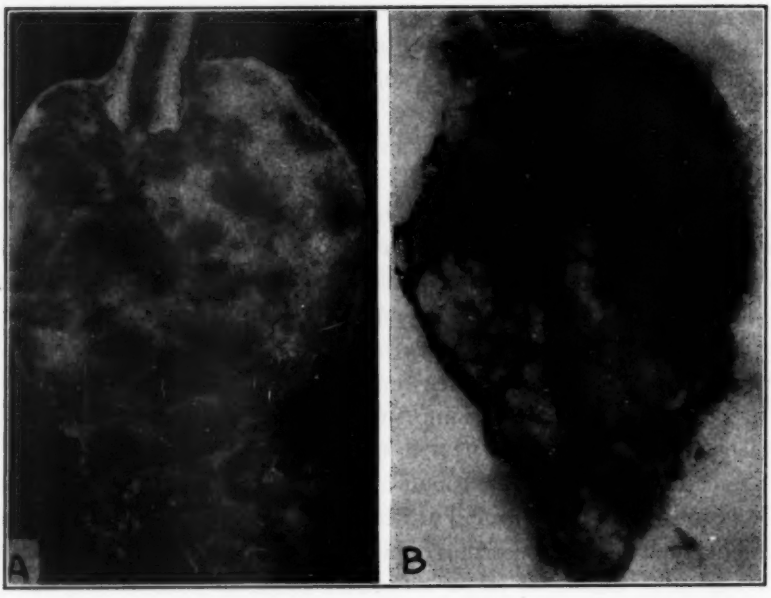

Fig. 1 A. Photograph of cut surface of distended anterior part of left 7th rib from a case of fibrous dysplasia in a woman of 35 in whom several other ribs and a number of vertebrae were also involved.

Fig. 1 B. Roentgenograph of sectioned half of the rib shown in Fig. 1 A. Note the multiloculated shadow. Actually, the interior of the rib is entirely filled with fibro-osseous tissue. The loculated shadow results from ridging on the interior of the cortical shell.

gone cystification.

In lesions or parts of lesions in which the replacement tissue in the interior of the bone is not highly osseous or is cystic in part, it will tend to cast a rather radiolucent shadow. In lesions or parts of lesions in which the replacement tissue has undergone extensive ossification, it will tend to cast a shadow resembling ground glass or spirals of smoke. If the replacement tissue has eroded the original cortical bone and distended the newly formed cortex, and if the latter has bony ridges on its inner surface, the affected area may present a "multilocular" appearance, although, as tissue examination has repeatedly shown, the area in question may actually be solidly filled by the basic fibro-osseous tissue.

Abnormal Cutaneous Pigmentation: Of the other manifestations seen

in cases presenting the fibrodysplastic skeletal lesions, the most common is abnormal cutaneous pigmentation. A pigmented skin area is not elevated, has the same texture as the rest of the skin, and is yellowish or yellowish brown. The discoloration reflects (as others also have found) the presence of an abnormal amount of melanin pigment, particularly in the basal cells of the epidermis, though some of the cells of the granulosa layer may also show pigment granules and an occasional pigment-bearing cell may likewise be seen in the corium. Otherwise, a pigmented skin area does not differ histologically, either, from the unaffected adjacent skin. We do not know, as yet, the explanation for the pigmentation.

An abnormally pigmented area may appear as a small uniform patch, a patch of clustered freckles, a large blotch, or a very extensive field. There can be no doubt that when the pigmentation is not extensive and the pigmented area or areas are light yellow, it may be overlooked, as indeed it was in one of our earliest cases. In a case of fibrous dysplasia which we saw recently, in which the skeletal involvement appeared to be limited to a single bone, the patient presented a number of abnormally pigmented skin areas. However, abnormal cutaneous pigmentation is certainly not seen in all the cases, and is thus not a necessary accompaniment of the fibrodysplastic skeletal changes. Indeed, the writer has seen some patients in whom the skeletal involvement was fairly severe but in whom careful search, including examination of the scalp and buttocks, failed to reveal a single patch or blotch. In such cases, one may, it is true, find some scattered individual freckles on the upper part of the back, or an occasional pigmented or vascular nevus. However, everyone recognizes the commonness of these in the general population, even at the younger age levels, and one cannot attach to them the same significance that belongs to a patch or blotch or to an area of pigmentation constituted by freckles gathered in a cluster.

Sometimes, the site of the abnormal pigmentation corresponds to that of severe skeletal involvement. However, the cutaneous pigmentation may be in a region where the bones are not affected. Thus, in one of our cases, in which the only focus of fibrous dysplasia was in the upper portion of the shaft of a femur, a patch of cutaneous pigmentation several inches in diameter was present on the dorsum of the foot on that side. In another case, in which the fibrodysplastic changes were in bones of the right lower limb bud, a single patch of cutaneous pig-

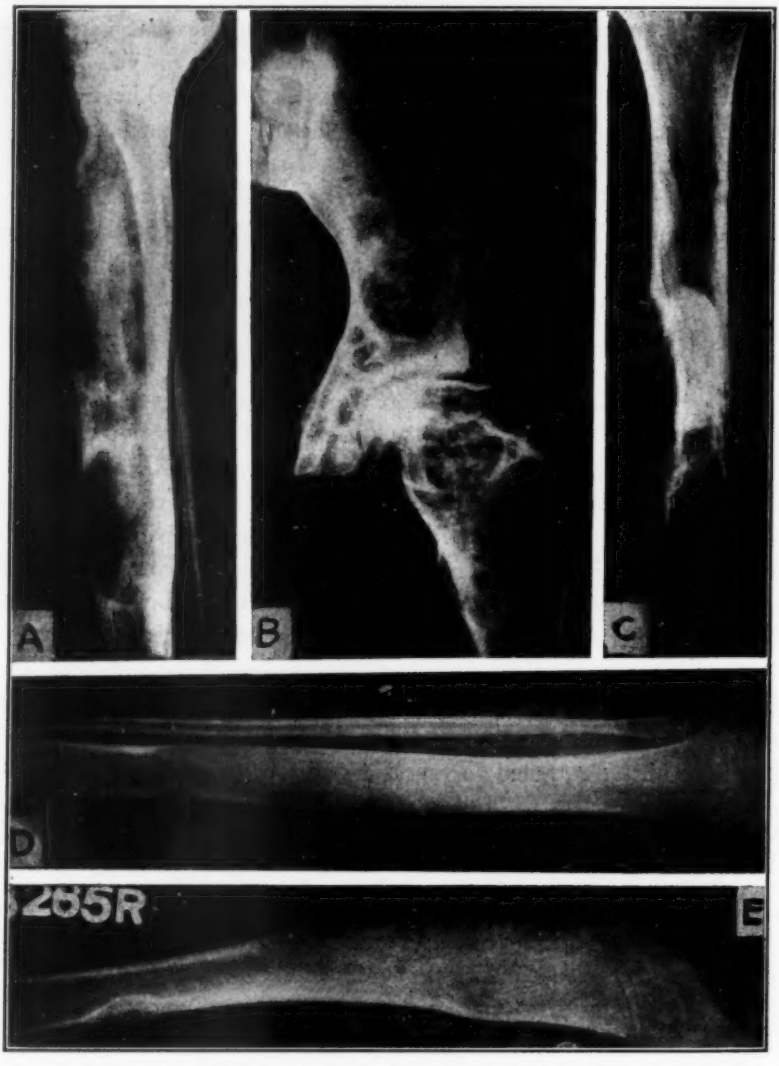

Fig. 2 A, B, and C. Roentgenographs of the left tibia, innominate bone, femur, and humerus, in a case of fibrous dysplasia in a girl of 24 in whom a number of other bones were also involved. Compare the multiloculated shadow cast by these bones with the appearance of the bones shown in figures 2 D and 2 E, which are from another case.

Fig. 2 D and E. Roentgenographs of the right tibia and femur in a case of fibrous dysplasia in a girl of 9 in whom the right innominate bone and some bones of the right foot were also involved. In this case, the affected bone areas cast a "ground-glass" shadow. This appearance is due, as tissue examination showed, to the presence of considerable new bone in the fundamentally fibrous replacement tissue.

mentation was found on the skin of the middle of the left leg.

Skeletal Precocity: In some cases, both skeletal growth and skeletal maturation (that is, the ossification and fusion of epiphyses) are accelerated. These two effects work at cross purposes. Thus, for a time during childhood, the patient may be excessively tall for his or her age and show a skeletal age several years in advance of the chronological age. However, because there is premature epiphysial fusion, the ultimate height of the patient is usually below the average.

Knowledge of the occurrence of the skeletal precocity has been derived mainly from cases in which the fibrodysplastic skeletal lesions were pronounced and associated with sexual precocity. However, Falconer, Cope, and Robb-Smith state that skeletal precocity may be present even in the absence of sexual precocity. Whether it occurs in the milder cases—for instance, those in which the bones of one limb bud alone are involved—is difficult to say, for often these cases do not come to light until near the end of the growth period. In one case of this type seen recently, in which the patient was a girl of 9, and in which I studied the x-ray films of the entire skeleton, I could not find evidences of skeletal precocity on the basis of the usual standards for measuring the same. This was true also in another recent case—that of a girl just 19 years of age in whom the fibrous dysplasia was apparently limited to a tibia but who also showed several patches of cutaneous pigmentation. In this patient, the skeletal age as evaluated from the epiphysis for the crest of the ilium and that for the ischium corresponded exactly to the chronological age. The basis for the skeletal precocity in those cases in which it is found is apparently some endocrine imbalance.

Sexual Precocity: We come now to the question of the sexual precocity found in a small proportion of cases of fibrous dysplasia—especially those in which the skeletal lesions are pronounced and extensive. This precocity was at first thought to occur exclusively among the female patients, but several instances of its occurrence in male patients also have now been reported.[9] In the female, it is manifested in catamenia at an abnormally early age (as early even as the first year of life), enlargement of the external genitals, and the appearance of secondary sex characteristics, notably the development of large breasts showing prominent areolae, and the growth of pubic and axillary hair. The onset of precocious menstruation often coincides, more or less, with the genital hypertrophy and the premature appearance of the

secondary sex characteristics. In the male, of course, the sexual precocity follows the male pattern. All the studies which have been undertaken in regard to the gonadotropic, follicle-stimulating, or estrogenic hormone content of the urine of these subjects have failed to yield any abnormal findings. Nor do the sex glands themselves show anything abnormal. Possibly there is, in these cases, an abnormality or lesion in the hypothalamus, conditioned by the fibrodysplastic changes in the skull. However, there is no basis for holding, as some[10] have held, that the fibrodysplastic skeletal lesions have their basis in the endocrine imbalance which necessarily underlies the sexual precocity. Finally, it is of interest in connection with the latter that there are a few recorded instances in which female patients who showed sexual precocity have later gone successfully through pregnancies and given birth to children who showed no signs of the disease.

Other Associated Phenomena Occasionally Observed: In an occasional instance of fibrous dysplasia, such diverse phenomena as hyperthyroidism, congenital arteriovenous aneurysm, rudimentary kidney, and visual disturbances from pressure atrophy of the optic nerve have also been observed.

Course of the Disease in the Skeleton

Tendency toward Stabilization: Our experience favors the belief that the period of active progression of the skeletal involvement tends to end when adult life is reached, in the sense that bones which were not involved by this time do not begin to become so now. Thus, even when fibrous dysplasia of bone is first uncovered in adult life, the skeletal lesions apparently date back to childhood. It is true that in a case showing extensive skeletal involvement already in childhood, one or more of the severely affected bones may show progressive deformity in adult life. However, this is due to weakening of the bone, and is not inconsistent with the appearance of increasing ossification of the fibrodysplastic tissue as another aspect of the process of stabilization. In fact, in some cases (particularly in the skull though also in some long bones) sclerotization of the fibrodysplastic tissue may become very pronounced. Indeed, it may progress to such a degree that the roentgenographic appearance of the affected bones may even suggest Paget's disease. Should such sclerotized tissue be subjected to anatomic study, it may actually be misinterpreted as representing Paget's disease, by one

not thoroughly familiar with the latter or with the nuances of the histopathology of fibrous dysplasia. At any rate, what we have said so far in general about stabilization of the bone lesions does not preclude the occurrence, in certain cases, even during adult life, of tremendous increase in size of the lesion in one or another of the affected bones, as will now be brought out.

Rapid Enlargement of the Lesion in One or Another Bone without Evidence of Malignant Transformation: The fact that lesions which may have been stabilized for years can take on some growth activity has been familiar to us for some time. Thus a patient may come in even during middle life because of complaints of only recent origin, due to a spurt of growth (perhaps quite slight) in a lesion which has clearly been present for decades. Relative rapid exuberant growth of one or more fibrodysplastic lesions is infrequent, but was illustrated in one of our cases. The patient was first seen at our hospital in 1940, when she was 35 years of age. She stated that when she was 9 she had a flow of blood from the vaginal region which persisted for 3 or 4 days, that she was given some medication by mouth for this, and that she had no further vaginal bleeding until the age of 16, when menstruation set in. She presented no non-elevated pigment patches or blotches, though she did show, on the skin, a number of small, scattered, elevated pigmented nevi and some vascular nevi. Her first difficulty relating to the skeleton appeared when she was 27 years old, in the form of a large lump on the left side of her chest and specifically in the left 7th rib anteriorly. This lesion was enlarging and had not been controlled by radiation, and she was admitted for its surgical removal. Roentgenographic examination now showed, however, that the posterior part of the left 7th rib was also affected, and that the 7th and 8th ribs on the right side were extensively involved, as were several dorsal vertebrae. The anteriorly affected part of the left 7th rib was removed by Doctor Leo Mayer, and beyond the costal cartilage the rib was found expanded to the size of a large pear by fibrodysplastic tissue of characteristic histology.

The patient was then well for 2 years, when, because of a spurt of growth occurring in the bodies of some of the affected vertebrae, she developed signs of pressure upon the spinal cord, at the dorsal level. At the surgical intervention, the compressing tissue which was growing out of the bodies of the dorsal vertebrae was removed, and the patient

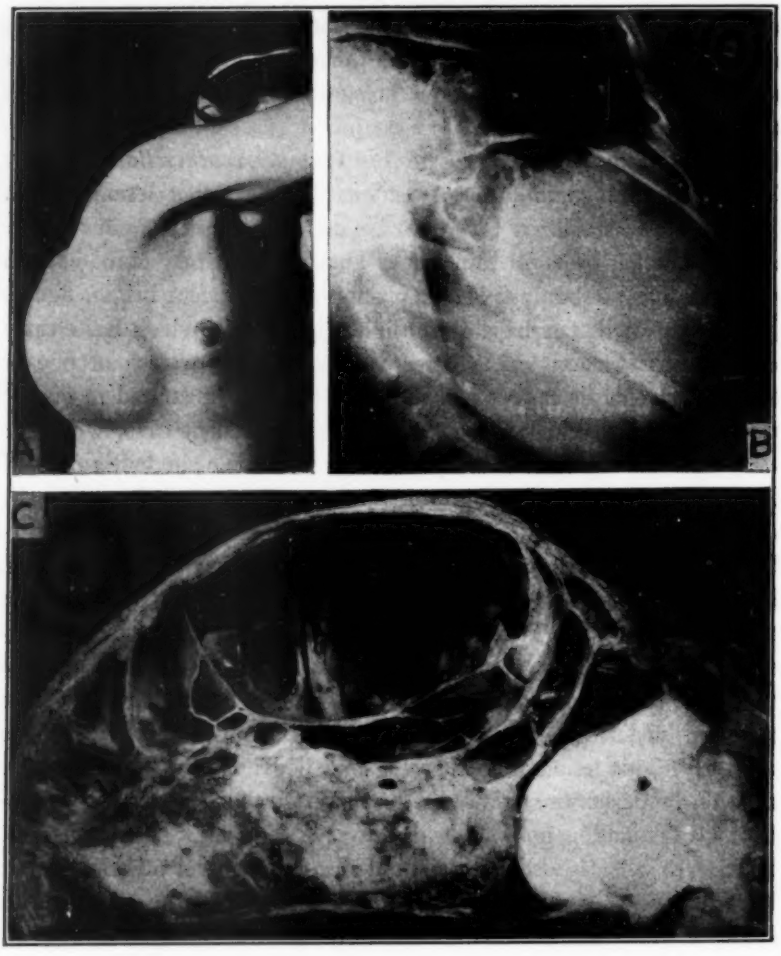

Fig. 3 A and B. Note the huge tumor mass on the right side of the chest. It was from this patient, now 40, that the left 7th rib shown in Fig. 1 had been removed 5 years earlier. At that time, the right 7th and 8th ribs were already known to be affected, but the tumor mass now present on the chest was not there then. It developed rapidly, in the course of a few months, as a result of progression of the previously existing lesion in the right 8th rib, as shown in Fig. 3 B.

Fig. 3 C. Photograph of sectioned tumorously expanded right 8th rib, which produced the appearance shown in Fig. 3 A. Note the cysts and the solid tissue below them. The ball-like mass to the right was composed of collagenous connective tissue with little new bone in it.

made a substantial recovery. In 1944, there was a recurrence of the cord symptoms, she was re-operated upon, and additional fibro-osseous tissue was again removed extra-durally from the dorsal region. The laminectomies were done at Mt. Sinai Hospital by Doctor Ira Cohen, and Doctor Paul Klemperer kindly gave me the opportunity of examining the slides from the material removed at both these interventions—tissue which showed the pathology typical of fibrous dysplasia. Also in 1944, but some months after the second laminectomy, the patient began to develop, on the right side of the chest a tumor mass which rapidly attained huge proportions. This mass resulted from a tremendous enlargement of the lesion which earlier films had shown to be present in the right 8th rib.

This rib, together with the fibrodysplastic 7th rib and the uninvolved 9th rib, were removed by Doctor Leo Mayer in one mass, which was approximately of the size of a standard football. When it was sectioned in its long axis, the exposed cut surface showed that fully half of the mass was represented by a huge multilocular cystic area in which some of the cysts were filled with clotted blood and others with yellow-green fluid. The rest of the mass was made up of one large oblong area, composed of quite gritty fibrous tissue, and one ball-like area of highly collagenous tissue with little if any grit in it. Though clinically we seemed to be dealing now with a sarcoma which had developed in a fibrodysplastic rib, the gross appearance of the lesion already made it necessary to reject this diagnosis. Furthermore, histologic examination of great numbers of tissue blocks from every part of the lesion also failed to show any evidences of malignancy. It is in harmony with these findings that during the 1½ years which have elapsed since removal of this great mass, the patient has felt in better health than she had had for many years before, and has gained in weight and strength.

Sarcoma Appearing in a Case of Fibrous Dysplasia: Until recently, we had neither seen nor read of any cases of fibrous dysplasia in which a sarcoma appeared. In 1945, Coley and Stewart[11] called attention to 2 such cases. In their first case—that of a woman 42 years of age when first seen—there was a massive osteolytic tumor of the left scapula, along with fibrous dysplasia in the skull, some ribs (particularly on the left), the left humerus, ilium, and femur, and the right pelvic bone and femur, associated with extensive abnormal cutaneous pigmentation. The tumor of the left scapula proved, on punch biopsy, to be a non-bone-forming

sarcoma, while examination of tissue from one of the ribs established the diagnosis of fibrous dysplasia in regard to the rest of the skeletal lesions. In their second case—that of a man 34 years of age when first seen—there was a massive tumor involving the left hip region, while the left pubic bone, femur, and tibia showed roentgenographic alterations consistent with a diagnosis of fibrous dysplasia. The tumor in the hip region proved, on punch biopsy, also to be a non-bone-forming sarcoma, while a biopsy specimen from the tibia showed evidences of fibrous dysplasia. The patients in the 2 cases survived for 11 and 4 years, respectively, and died presumably from metastases, but in both cases the course run by the primary malignant tumor was unusual in that small doses of radiotherapy apparently held it in check for a long time.

Since publication of the paper by Coley and Stewart, the writer has studied material from a case of fibrous dysplasia involving bones of the right lower limb, in which a sarcoma developed in the fibrodysplastically involved tibia. The limb was amputated through the middle of the femur, and I was able to study, both grossly and microscopically, a longitudinal half of the removed femur, tibia, and fibula, through the courtesy of my colleague Doctor (now Major) Charles Sutro. Doctor Sutro plans to report this case in detail. Here a very brief sketch will suffice. The patient was a man of 25, whose first difficulty relating to his skeleton was of only a few months' standing and consisted of some pain in the right leg and the appearance of a slowly enlarging swelling in the middle of the tibia. Roentgenographic examination revealed the presence of fibrous dysplasia, of which, as noted, the patient was entirely unaware, involving the right femur, tibia, and fibula, and of a bone-forming sarcoma more or less in the middle of the shaft of the tibia. Both grossly and histologically, the sarcoma proved to be an osteogenic sarcoma. Below the sarcomatous area, the marrow cavity of the tibia contained non-sarcomatous fibro-osseous tissue such as one sees in sclerotized fibrous dysplasia lesions. Similar tissue was observed in the marrow cavity of the femur specimen and fibula specimen. However, even in the tibia, in the region of junction between the sarcoma and the fibrodysplastic tissue, the latter showed nothing which could be interpreted as representing presarcomatous transformation of the fibrodysplastic tissue. Thus, all that one could safely say about this case is that an indubitable osteogenic sarcoma developed in the tibia, which latter still showed evidences of fibrous dysplasia.

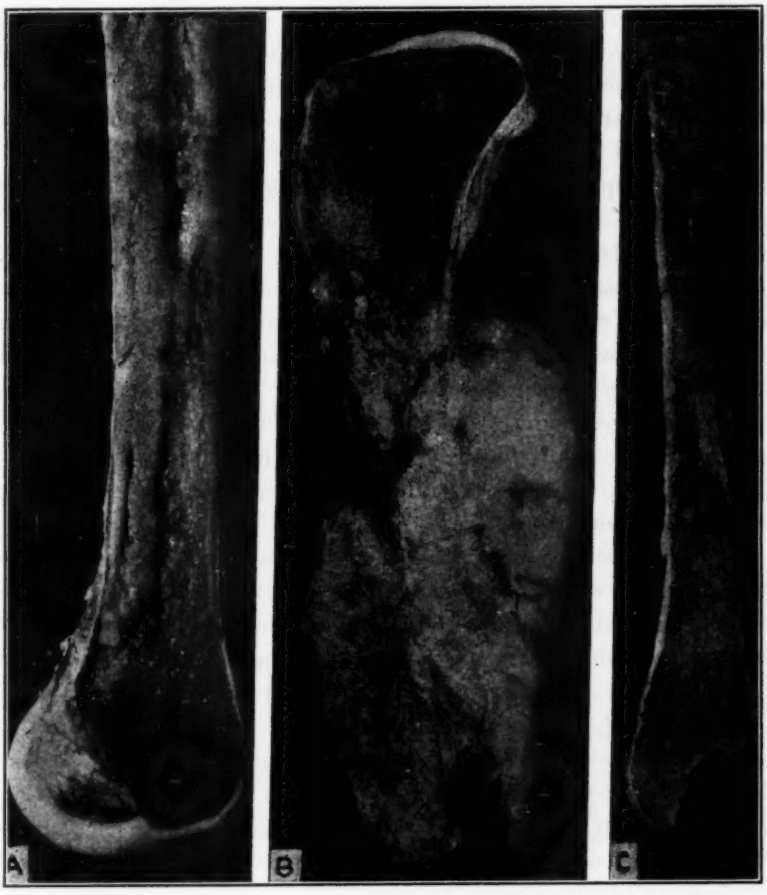

Fig. 4 A, B and C. Photographs of part of femur, tibia, and fibula, respectively, from the right lower limb of a man of 25. There is an osteogenic sarcoma (Fig. 4 B) in the tibia, while the femur (Fig. 4 A) and the fibula (Fig. 4 C) show tissue characteristic of fibrous dysplasia in their interiors. There was evidence of fibrous dysplasia also in the lower half of the tibia which was the site of the osteogenic sarcoma.

Diagnosis and Differential Diagnosis

The diagnosis of fibrous dysplasia can usually be made on clinical grounds, including the roentgenographic appearance of the affected bone or bones. This is particularly true when a number of bones are involved. The tendency of the involvement to be restricted to the

bones of one limb bud or at least to be predominantly on one side of the body is another valuable criterion. When only one bone or part of one bone is involved, definitive diagnosis has to rest on tissue examination, since in such cases the roentgenographic differentiation between fibrous dysplasia and solitary bone cyst, enchondroma, or even a fibroma of bone cannot always be made. Some (for instance Dockerty and his associates[12]) imply that one cannot make a diagnosis of fibrous dysplasia on the basis of a bone biopsy examination alone, and in particular that one cannot differentiate on this basis between the histologic picture of fibrous dysplasia and that of hyperparathyroidism. The fact is, however, that the essential pathologic picture presented by an adequate bone biopsy specimen is different in a case of fibrous dysplasia from what it is in hyperparathyroidism. Indeed, if the examiner has a firm grasp on the pathology of the bone lesion in fibrous dysplasia, he will easily be able to distinguish it not only from the bone lesions of hyperparathyroidism, but from all other bone conditions, on the basis of histologic examination.

In cases of fibrous dysplasia, the only aberration which one may find in the blood by clinical biochemical analysis is an elevation of the serum alkaline phosphatase activity value. Though in some cases, in spite of the fact that many bones are involved, this value is hardly above normal, in other cases we have found it as high as 17 or even 20 Bodansky units. The fact that the serum calcium value is never elevated in fibrous dysplasia immediately differentiates it on this basis alone from hyperparathyroidism. In cases of fibrous dysplasia in which mineral balance studies (calcium and phosphorus) have been done, these have always yielded values within the normal range, which is again not what is encountered in hyperparathyroidism.

In the writer's experience, the only condition which can sometimes raise the problem of differential diagnosis on a clinical basis is skeletal enchondromatosis of the Ollier type—that is, enchondromatosis limited to some bones of one limb bud or involving predominantly the bones on one side of the body. However, in these cases, if hand or foot bones are involved, the punched-out rarefactions in the shafts of the phalanges and metacarpal bones and the bulging of the contours of some of them, as seen roentgenographically, are almost sufficient in themselves to show that the condition is enchondromatosis. Anatomically, of course, in the latter, the abnormal tissue occupying the interior of the affected bones

is basically hyaline cartilage, so that there is no possibility of confusion with the abnormal tissue in the interior of bones affected with fibrous dysplasia.

Finally, in respect to differential diagnosis, we come to the contention of some that fibrous dysplasia of bone is not a disease entity at all, but a variant of some other disorder. Thus Snapper[13] maintains that it is to be linked with Hand-Schüller-Christian's disease (lipoid granulomatosis) as an atypical clinical expression of that disorder. However, the clinical, roentgenographic, topographic anatomic, and histologic anatomic differences between the two disorders are so great that there should be no confusion between them. The distinctions have already been emphasized by the present writer[14] in another connection. In that connection, he devotes attention mainly, however, to the lack of validity of Thannhauser's contention[15] that fibrous dysplasia of bone (or, as he prefers to call it, osteitis fibrosa cystica localisata et disseminata) is not an independent entity, but is to be related by its clinical and histological features to neurofibromatosis of Recklinghausen. Here it will suffice to point out again that the skeletal lesions which are the central feature of fibrous dysplasia of bone find no counterpart in the skeletal aberrations occasionally found with neurofibromatosis.

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SURGICAL PRINCIPLES IN WOUND MANAGEMENT*

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THE wounds of warfare vary but little from those of civil life except in two respects: first, they occur in epidemic form, and, second, there is a special group caused by high velocity missiles. Such missiles produce an explosive effect within the tissues, with the lines of force extending in an oblique, radiating fashion. Such a wound consists of three zones: (1) the wound track itself with its debris; (2) a zone of devitalized tissues; and (3) an area of contused cells and hemorrhagic exudate.

We often think we have discovered something new, only to find that we are merely reaffirming old principles. Man has forever sought some panacea to place on or in a wound to insure its healing, and all sorts of applications and concoctions have been used. We have run the whole gamut of boiling oil and cracked ice, of polypharmacal lotions, ointments, and complicated chemicals, of light rays and gases, of vegetables and minerals, and of animal life and material both quick and dead. Eventually all these drop into their proper places, and fundamental principles reassert themselves.

THE PAST

In the year 1214 the city of Bologna made contract with a certain Ugo of Lucca to perform the surgery for six months of each year, and in case of war to treat the soldiers free.[1] Ugo was already past middle life and it is not defintiely known where he obtained his medical education. He had four children, three of whom practised medicine in Bologna, and the oldest of these was Teodorico, who learned his medicine from his father and was destined to become even more famous. Both Ugo and Teodorico made their greatest contribution to modern

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surgery in the refutation of the belief that pus in a wound is good. Teodorico (Theodoric, A.D. 1205-1296) urged simple cleanliness, the avoidance of drains, and recommended simple dressings of wine compresses and plain gauze. He did not use the cautery and paid much attention to the general nutrition of his patients.

"For it is not necessary," he says in his *Surgery* written in 1266, "as Roger and Roland have written, as many of their disciples teach, and as all modern surgeons profess, that pus should be generated in wounds. No error can be greater than this. Such a practise is indeed to hinder nature, to prolong the disease, and to prevent the conglutination and consolidation of the wound. . . . Pus destroys and increases the size of a wound."[2]

Medicine and surgery at this time sorely needed reform from the Galenical principles of salves and tents and the polypharmacy then so rife, and this change was taught by Theodoric, "who produced beautiful scars without the use of any ointment."[2]

One of his contemporaries was William of Saliceto who held similar views against the theory of "pus laudabile." Less is known of him but his most famous pupil, Lanfranc of Milan, pays him high tribute. Lanfranc, writing in Paris in 1296, states that the wound should be clean and dry and bleeding should be controlled by ligature if necessary; drains, or "tents," should not be used, and one must be careful to include all layers in the suture so as not to leave a dead space. He advised that a powder, one of the ingredients of which was lime, be employed as a dressing so as to keep the wound dry.[3]

The most famous pupil of Theodoric was Henri de Mondeville, the greatest of the early French surgeons. De Mondeville studied with Theodoric and carried that master's philosophy of the surgery of wounds back to France with him. It is not clear whether or not he ever worked with Lanfranc, then settled in Paris, but he refers to him with considerable respect. As one of the royal surgeons under Philip le Bel he was also associated with Jean Pitard, who apparently believed in the same surgical principles. De Mondeville appealed for cleanliness, hemostasis, and for simple careful dressings which should not be disturbed for several days. Should heat and pain develop, then the wound must be reopened and washed out again or poultices applied. Needles should be triangular, sharp and clean, "or they will infect the wound,"[4] and there should be grooves by the sides of the eye so that the thread

would not cause further damage as the flesh was pierced. Every cause of the formation of pus must be avoided. His comments were somewhat caustic as he said that "many more surgeons know how to cause suppuration than to heal a wound,"–[4] a statement that held true for six hundred years.

But this courageous little group marched with a flickering light through the darkness of the period. They flowered in the earliest dawn of the Renaissance, for over a century from 1214-1325, but finally, with the death of de Mondeville, the light went out, and with Guy de Chauliac there was a return to the Galenical theories of salves, tents, and laudable pus. At a time when it was dangerous to express one's views and against the strong opposition of the medical world they had the courage of their convictions and it was not until almost five hundred and fifty years later that Lister finally proved to the world that these truly remarkable men–Ugo da Lucca, Theodoric, William of Saliceto, Lanfranc, and de Mondeville, were right.

As we pass through the Renaissance we come upon a new kind of wound, that caused by gunshot, first mentioned by John of Vigo in 1514 and later in the same century studied more carefully by Paré. He was the first to attempt to trace the course of bullets by placing the patient in the position he was in when hit, and also recognized that the effects of a gunshot wound were chiefly due to contusion and laceration rather than to burning and actual poisoning of the tissues. He turned away from the use of the cautery and boiling oil in these wounds and improved the ligature, thereby reducing secondary hemorrhage, and so made major amputations possible with comparative safety.[2]

Notwithstanding the progress in anatomy, physiology, pathology and physics and the discovery of the microscope and "animalculae" by van Leeuwenhoek during the seventeenth century, surgery remained almost completely static. Still another hundred years later we find John Hunter, in his extensive treatise on wounds, admitting that wounds with external communication commonly inflame and suppurate and further if ligatures are used, wounds *will* suppurate. In considering the possibility of primary healing he says that "this method is probably limited to some certain distance of time after the wound has been received . . . perhaps the sooner it is done, the better."[5] Plaster he considered to be superior to sutures as there was less danger of suppuration. Tension, he thought, was the natural consequence of wounds and

no better results were obtained by opening gunshot wounds, though each wound should be judged of itself.

The observations of Semmelweis and Pasteur prepared the way for the final vindication of the tenets of Theodoric and de Mondeville by Lister in his original work with phenol and phenol paste on compound fractures. In his report in 1867 he says:

"All the local inflammatory mischief and general febrile disturbance which follow severe injuries are due to the irritating and poisonous influence of decomposing blood or sloughs." The initial antiseptic dressing was to protect the wound from infection from without but after the first dressing the object in contact with the tissues should be as bland and neutral as possible.[6]

"Injured tissues do not need to be 'stimulated' or treated with any mysterious 'specific'; all that they need is to be let alone."[7] He further recognized the danger of tension by pointing out that it is sometimes well to avoid stitching and the tension that may be associated with it, and a clean blood clot which contracts makes an excellent dressing.[8]

Building upon the firm foundations of Lister a young American surgeon, W. S. Halsted, in 1891 enunciated the fundamental surgical principles in the healing of wounds. At this time Lister was then 64 and his great work had already been accomplished; Halsted was but 39 and was on the threshold of his brilliant career. He saw fully what the work of Lister had made possible and realized that the field of surgery should and could be extended still further by more careful handling of the tissues and attention to detail. Infection was now understood, true, but it was by no means well controlled. In his initial article on the treatment of wounds Halsted says, referring to Lister:

"He has taught us what can be done under the cover of antiseptics. One may maltreat the tissues to any extent—mutilate the wound during the operation in every possible way, cut off by ligatures the circulation in large masses of tissue, produce extensive areas of superficial necrosis by irrigation with antiseptic solutions, stuff the wound with gauze and drainage tubes, tear out the stuffing and with it the granulations which have grown into it, restuff, etc.—and still the wound may heal without suppuration, without septic inflammation, and in a way which is, perhaps, altogether satisfactory to the surgeon."[9]

By this statement Halsted well judged the temper of the average surgeon as he rushed into the new fields of surgery that had been

opened by Lister. Both the dangers and future possibilities were clearly understood by Halsted in his approach to and establishment of our present aseptic surgery. He turned away from catgut to the silk ligature because silk was more uniform and could be completely sterilized. Silk being non-absorbable, unless strict asepsis and great attention to detail were practised, clean healing would not result and foreign body sinuses would persist. This could be avoided, however, by a proper technique. The essential principles in the treatment of wounds then, are: (1) the employment of fine sutures; (2) delicate handling of the tissues; (3) partial obliteration of dead spaces; (4) not irrigating the wounds with disinfectants or using mass ligatures or drains; and (5) applying dressings with gentle even pressure.[9] For many years these measures were considered by many as meticulous and unnecessary, but as the standards and scope of surgery have increased these precepts have gradually become generally accepted.

In military surgery a similar evolution in the treatment of wounds was developing as the important role of foreign bodies and dead tissue in the causation of infection became increasingly apparent. This is admirably described in the British official history of the Great War:

"The treatment of wounds by free excision at the casualty clearing stations was generally adopted as an alternative to the use of free incisions for drainage, and after the year 1915 it became a common practice during quiet periods. It could not, however, be employed at that time during a battle because of the small size of the clearing stations and the scarcity of their surgical personnel, and it was not until the first battle of the Somme in 1916 that it began to be adopted at the front on a large scale. From that time on it was the regular practise, and was proved to be the most efficacious means for the prevention and arrest of gas gangrene. The earlier this treatment was carried out and the more thorough the removal of all torn muscle and foreign bodies, the more satisfactory were the results, and during the heavy fighting of the year 1917 the large majority of all the severe wounds were treated in the casualty clearing stations by this method. Only when the numbers of wounded became too great were such patients sent to the base before operation. It was found to be most important not to excise any skin, although free incision to get at the deeper parts were commonly required. . . .

"*Suture of Wounds.*—The wounds treated by suture in the early

days of the war did badly, and as a result the closure of wounds fell into complete disuse for the next year or two. In 1917 suture was again tried, but then only under good aseptic conditions and after the excision of damaged tissues and the removal of all foreign bodies, and it was soon found that under these conditions very good results could be obtained."[10]

The greatest surgical advance that emerged from the First World War was the debridement of wounds. This principle was promptly adopted by us and in our own official history Pool says:

"The ideal treatment of war wounds, as based on experience gained in the World War, consists in complete excision of all devitalized tissue, followed by the application of immediate or secondary suture, according to conditions existing in a given case."[11]

The Present

As surgeons we must treat wounds caused by trauma and we must ourselves make wounds, for the performance of elective surgery and for the treatment of infection. Hence we must be interested in the repair of tissues and the healing of wounds subsequent to trauma and of our own fashioning. Tissue repair is a complex biological process, but one that we can favor or hinder according to our own actions. The ideal and least complicated wound is the non-penetrating variety involving only skin and subcutaneous tissues. Certain tissues have enormous powers of regeneration,—the corneal epithelium or liver parenchyma; some, such as cartilage and striated muscle, regenerate very slowly and repair occurs almost entirely by fibrous scar; and in some repair takes place in a dual manner, as in smooth muscle.[12] This inherent ability of regeneration by the tissues themselves varies considerably with age; in the lung, for example, there is probably true regeneration and hyperplasia in youth, whereas in adult life there is none.

Normally the healing of a wound is brought about by the movement and proliferation of living cells and by contraction.[13] When healing is complete this growth of new cells stops. Healing itself may be by apposition, as in primary union, or by granulations and scab formation. Initially there is always a certain amount of traumatic inflammation varying with the extent of tissue trauma, contamination, sloughs and foreign bodies that may be present. This exudate consists of blood,

the wound secretion or plasma which is rich in fibrinogen at first, and surrounding edema. In the fresh cleanly incised superficial wound, opened and closed under aseptic and atraumatic technique, this exudate is minimal and as the edges are apposed, this secretion of plasma—the "wound balm" of Paré—agglutinates them and forms a thin cement substance, which maintains healing until the tissue repair itself takes over. With such a wound this latent period is short and has a fairly uniform time of four to six days.[14] This quiescent phase is an initial period of healing common in all tissues. It was noted by Carrel first in 1910 and further elaborated in 1921,[15, 16] and depends upon both local and general factors. The local factors are: (1) the amount of killed or damaged tissues in the wound surfaces and in the walls or immediately surrounding zone of the wound; (2) the vascularity of the tissues involved; (3) the integrity of the blood flow to the damaged tissue; (4) the exudate in the wound and adjacent tissues; (5) the number and character of the infectious organisms present; and, (6) the number and character of the foreign bodies to be extruded or encapsulated.[17]

The general or systemic factors that influence wound healing are: (1) the age of the tissues, already mentioned; (2) normal hydration, dehydration, over-hydration; (3) the general nutritional state; (4) avitaminosis; (5) the state of the circulation and the blood picture.[17]

During this earliest phase of repair the wound is being cleaned up by tissue destruction through autolysis from enzymes liberated by the cells themselves, by heterolysis from enzymes liberated by the leuhocytes in the necrotic zones, and through the action of macrophages in removing cellular debris and in surrounding foreign bodies.[18] This latent, or destructive, phase is the most dangerous period in wound repair. It is prolonged by the presence of infection, debris, foreign bodies, sloughs, devitalized tissue and impaired circulation, all of which may be directly influenced by the surgical treatment of the wound. From the systemic standpoint this phase is prolonged by any of the factors already noted. True, the surgeon is powerless to influence the age of the tissues but by assuring a normal state of hydration, a well balanced high protein diet with sufficient vitamins, particularly C and B, and a normal blood picture, he can go far in compensating for the old age of the tissues. Furthermore, wounds do not heal well in the presence of severe anemia or a damaged circulation.

The second important stage in wound healing is the phase of fibroplasia, at which time active repair commences with abundant proliferation of fibroblasts. In the fresh clean wound this continues from about the fourth to the fourteenth day and it is during this time that the tensile strength of the wound is developed. The curve rises rapidly at first, reaching its maximum in ten to fourteen days.[12] From the practical standpoint this is the important criterion of an healed wound.

The constructive period, or phase of fibroplasia, begins very early and overlaps the destructive phase. What the actual stimuli are to wound repair is not well understood. It is thought by some that the diminished oxygen tension in the cells of the ischemic zone stimulates cell division. There may be some substance liberated in the process of cell destruction and numerous specific substances have been listed: embryonic or leukocytic extract, hormones, temperature, pressure, peptones, the sulphydryl radical, glutathione, hemoglobin, solar ultraviolet rays and others. Within the first few hours there is a beginning migration of cells to the site of trauma with gathering and budding of the endothelial cells of the nearby vessels, the presence of leukocytes, histiocytes, macrophages and fibroblasts, and the ameboid movement and mitosis of the epithelial cells. By the second day in primary healing rapid proliferation of these cells is evident; in secondary healing, filling with granulation tissue commences in six to eight days. While destruction is still in progress, however, there is but little fibroplasia and connective tissue fibrils do not appear.

Loeb (cited by Whipple) emphasizes "the importance of two processes in this stage of the lag period connected with the ameboid movement and proliferation of the invading fibroblasts. The first is the phenomenon of stereotropic response of growing cells to surfaces. Fibroblasts in contact with fibrin strands or fibrils have a strong tendency to elongate and grow along the fibrils, just as epithelial cells show ameboid movement along plane surfaces of granulation tissue or beneath the scab. The second reaction is a centrifugal force which directs the cells away from their own tissue and into the plasma mass in the wound space. This induces various kinds of cells, including fibroblasts, to move into the clot in a fan-like manner to take part in the organization of the clot. Similarly, endothelial buds show a centrifugal growth into the organizing fibrin with a spread of the vascular bed and thus enter into the formation of granulation tissue."[17,19]

The third and final phase in the cycle of wound healing is that of maturation. It is in this later stage that the cells mature, the wound solidifies and contraction occurs.[14]

If one studies histologic sections made at frequent intervals from a series of identical clean wounds, these changes are readily seen and may be followed through to the gradual elongation of the fibroblasts, the appearance of connective tissue fibrils, the disappearance of the cellular reaction and vascular granulation tissue, and the final appearance of collagen and the contraction that accompanies scar formation.

Other changes that occur in the course of healing are: (1) at first there is an increase in the fluid content with increase in the electrolytes; (2) there is a demonstrable, though slight, difference in electric potential in the wound; (3) due to local stasis there is local anoxia and increased CO_2, resulting in a faintly acid reaction initially; and (4) there is an early decrease in the tissue metabolism, which rises, however, with the advent of granulation tissue, blood and cells, and then slowly returns to normal as the wound heals.[18]

From the practical surgical standpoint, if one will but visualize and think of what is taking place in a wound, particularly in the destructive phase and lag period, the need for very careful surgery at once becomes apparent. Also, one will understand the different problems of delayed primary suture between the fourth and seventh days, between the tenth and fourteenth days, and the late secondary suture of old wounds, whether formerly grossly infected or not.

In order to provide the optimum wound the following factors are of prime importance: (1) Dissection with a sharp knife. (2) Complete hemostasis. (3) The maintenance of as sterile a field as possible. (4) Protection of the wound edges with towels, and exposed surfaces with moist abdominal pads. (5) The use of as fine ligature material as possible, with not more than twice the tensile strength of the tissue in which the suture or ligature is placed. (6) Minimum trauma with maximum maintenance of the blood supply and nutrition of the tissues.[20]

These criteria of Whipple may be elaborated by adding:

1. Protection of the blood supply, which consists of: (a) assurance that the main supply to the part involved is intact or as adequate as possible; (b) the avoidance of tension in the wound and of strangulation of the tissues by too tight sutures. These are perhaps the two most common errors of the surgeon. Strangulation may be caused by

tension as in intestinal distension following anastomosis; this may be prevented by nasogastric drainage and the use of the Miller-Abbott tube.

2. Reduction to a minimum of the foreign material left in wounds. It is not always remembered that ligatures, drains and packs, although required by the objectives of surgery and proper hemostasis, are actually foreign bodies.

3. The avoidance of mass ligatures and the devitalized tissue they cause.

4. The obliteration of dead spaces.

5. The application of dressings with even pressure. Such a dressing helps in maintaining hemostasis, protects the plasma coagulum, and obliterates dead space.

6. Rest of the part, by splints if necessary, even for soft part wounds.

7. The wearing of masks by surgeons, nurses, and attendants during the performance of surgery and at *all dressings of open wounds*. At the time of the armistice, in 1918, it had already been noted by the British that many of the nurses and orderlies were carriers of streptococci in their throats.[10]

When dealing with the traumatic wound, one can add little to Reid's dictum, that "it is the duty of the surgeon to remove all foreign bodies or dead or devitalized tissues, which are excellent encouragement to the growth of bacteria."[13] The crux of the debridement is the removal of *all* dead and devitalized tissues, debris, and foreign bodies. Bacteria increase in debris and necrosis, and a blood clot in such wounds soon becomes an infected slough. In the initial treatment of these wounds there may be deep pockets, as about a fracture, in which wound secretions and blood may puddle. This, and also the deleterious pressure effects of such an hematoma, may be prevented by providing dependent drainage for one to three days. All of this was clearly stated by Churchill in a letter on Wound Management:

"The keystone of successful wound management is the initial surgical operation. When this is performed correctly the complications of infection are absent or minimal and secondary suture may be carried out promptly and successfully. . . . .

"Use fine hemostats. Use the finest ligatures compatible with the procedure. Include the smallest amount of tissue in ligating a bleeding point. Do not repeatedly bite the wound with tissue forceps. Sponge

gently with pressure instead of wiping. *Remaining devitalized tissue produced by the missile or by the surgeon must slough before the wound can be closed by secondary suture.*

"Large wounds in regions of heavy muscles particularly when complicated by comminuted fracture require especial care. The depths of these wounds must be opened by a long incision with counterincision if necessary to allow free drainage of blood and tissue that may not be identified as dead at the time of debridement." [21]

Bactericidal agents are always harmful to the tissues when used in wounds. In infections, however, the harm to living cells may be outweighed by their value in the control of the infection and it is obvious that in the treatment of such infections some of the principles of surgery of wounds may have to be sacrificed temporarily in order to save life.[18] In World War I more than twenty different antiseptics were used in the ever present hope of finding some means of sterilization and selective chemical debridement of wounds. Some have been discarded altogether and the others have dropped into their correct position as adjuvants in the control of established infection.

When the bacteriostatics, the sulfonamides and penicillin and streptomycin, are employed, it should be realized that whatever their action, it is purely ancillary to, and never can replace, surgery. In the presence of slough, dead tissue and infected clot their action is nil. Administered systemically they are of great value in preventing the extension of infection and in the preparation of patients for wound revision and other surgery.

General Factors. The general factors that enter into the repair of wounds and that are under the control of the surgeon are hydration and electrolyte balance, circulation and the blood picture, nutrition and the vitamins.

Hydration: There is an intimate relationship between hydration, blood volume and circulation and unless the complete blood picture is considered in relation to, and corrected in accordance with, the existing state of hydration, serious mistakes in treatment may occur. Furthermore, what is considered normal hydration for certain cases, such as an abdominal wound complicated by peritonitis, might well result fatally in a wound of the thorax with disturbed cardio-respiratory physiology. Over-hydration must be avoided both because of the harm it may do to the patient generally, and specifically, because it interferes

with wound healing and prolongs the initial period of lag. Proper balance in the electrolytes should likewise be maintained and caution exercised not to overload a patient with normal saline solution, for instance, when he has no need of added chlorides, since this will eventually lead to edema and over-hydration due to the retention of the fluids in the tissues because of the excessive salt intake.

The Circulation and the Blood: It is essential that the circulation be competent in order to assure wound repair as edema and anoxia both impede it. Severe anemia produces a tissue anoxia, and with the ready facilities for hematocrit, hemoglobin, and plasma protein determinations now available to us by the copper sulfate method the blood status should be known and followed and any deficiencies promptly remedied by transfusions, both preoperatively and postoperatively. Anemia will almost always be present when one is dealing with major trauma, and, quite apart from the problem of adequate resuscitation, blood will probably also be required to overcome it.

Nutrition: Nutrition profoundly influences the repair of wounds. A high protein diet favors and a high fat diet retards it. Large amounts of protein are necessary at first and in the presence of infection with copious exudate and sepsis the dangers of hypoproteinemia are well known. In the diabetic the problem of diet assumes large proportions in its relation to the repair of tissues and infection. Of recent years nutrition has taken on added significance because of the large numbers of people on a starvation or near starvation ration with evidence of early famine edema and avitaminosis. A few sentences may be quoted from a report of conditions in a Prisoner of War camp in Luzon:

"And above all, we encountered malnutrition. Its alleviation took precedence over all but the most dire surgical emergencies, and the associated anemia and hypoproteinemia handicapped the response to the most ideal surgical treatment. * * * * The healing of open wounds and ulcers progressed only when the nutritional state of the patient improved."[22] Obviously the best way of providing adequate nutrition is by an abundant and varied diet. Where this is not possible, however, best use must be made of the available tools. Thus transfusions, plasma, protein hydrolysates by vein or tube, intravenous glucose and tube feedings will be of great value until a normal diet can be taken. The important thing is to continue some form of nutrition, for saline and glucose infusions alone are insufficient.

Vitamins: What has been said about nutrition applies also to vitamins. We are well aware of the role played by vitamin C in repair of wounds and the needs of the body for A, B, D, and also K under certain conditions. Many people on their usual diets may show some degree of vitamin deficiency. The original C-ration as supplied to the Army in 1942 and 1943 was notably low in vitamin C. So in the initial stages of wound repair adequate vitamin therapy must be provided to assure healing.

Summary

Seven hundred years ago the principle that wounds should heal *per primam* was enunciated by Ugo of Lucca. After an hundred years, however, this heretical opinion was overriden and surgery went back to the Galenical theories of *pus laudabile* and polypharmacy, not to emerge again until the last half of the nineteenth century under the leadership of Baron Lister, who firmly established antisepsis and then asepsis.

In 1891 William S. Halsted taught the modern principles of wound healing.

Our present conceptions are based upon his teachings. The points in the surgery of the wound and its repair are sharp dissection, gentle handling of tissues, complete hemostasis, maintenance of blood supply, avoidance of tension and strangulation of tissues, obliteration of dead spaces, the use of fine ligatures, the *excision of all devitalized or dead tissue and sloughs*, the removal of foreign bodies, and the application of a nonconstrictive dressing of even pressure.

In the cleanly prepared wound bactericidal agents are not only not indicated but do harm rather than good.

It is not necessary to "stimulate" healing. This will progress normally provided a wound is properly prepared, left clean, and dressed with a simple supportive dressing, and provided the patient is maintained in a normal balance as to hydration, blood picture, nutrition and vitamins.

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